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Synthesis of 2,3,6,8-Tetrahydroxybenzofuro[3,2-*b*][1]benzopyrylium Chloride (*Riccionidin A*)

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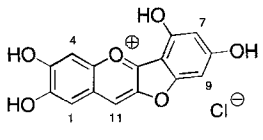
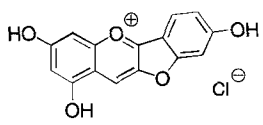
Abstract. The liverwort pigment riccionidin A (**1**) was synthesized in a single preparative step from simple starting materials by a double condensation reaction.

Riccionidin A (**1**) is a red to violet cell wall pigment found in the liverworts *Ricciocarpos natans, Marchantia polymorpha, Riccia duplex* and *Scapania undulata*. Its structure was elucidated in 1994 by Becker *et al.* [1] by analyzing 20 mg of the purified compound isolated from 550 g freeze-dried plant material.

1 is related to a few other naturally occuring anthocyanidins [2] such as morinidin chloride (**2**) [3] which have an oxygen bridge connecting the B- and the C-ring and giving rise to a benzofuran moiety. Thus, this type of pyrylium salts combines structural features of two important subclasses of flavonoids: the typical aryl substituted benzopyrylium unit of the anthocyanidins **3** [2] and the benzofuran moiety of the aurons **4** [4]. With hydroxy substituents in positions 2, 3, 6 and 8 *riccionidin A* (**1**) exhibits a unique substitution pattern. In all other naturally occuring benzofuro[3,2-*b*][1]benzopyrylium salts known so far the hydroxy and methoxy substituents are located in positions 1, 3 and 8. The synthesis of **1** prones the reported structure, and at the same time provides starting material for the synthesis of *riccionidin B* [1], a natural product whose actual constitution is unknown but is believed to derive from an oxidative dimerization of *riccionidin A* (**1**).



1



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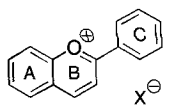

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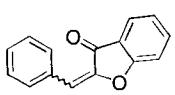

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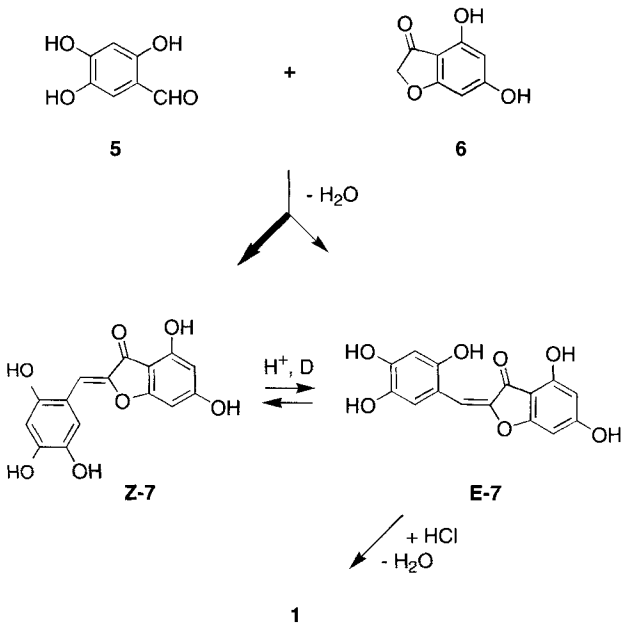
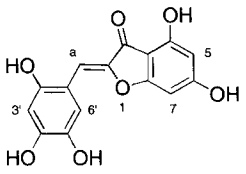


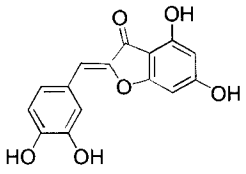
A one-step synthesis starting from the simple precursors **5** [5] and **6** [6] under acidic conditions at moderate temperature was envisioned in analogy to the formation of similar pyrylium salts [7]. However, after 3 h at 50 °C in acetic acid saturated with hydrogen chloride only trace amounts of **1** were detected. Instead, the auron **Z-7** was isolated as the main product identified by comparison of its NMR spectra with reported data of aureusidin **Z-8** [8] (Table 2), a very similar natural product lacking the hydroxyl group in 2'-position [9].

Tab. 1 Synthesis of **Z-7** and **1** from **5** and **6**; optimization of the reaction conditions: acetic acid as solvent, 1–5 h saturation with gaseous HCl (t_{HCl}), 1–125 h overall reaction time ($t_{overall}$); determination of product ratio by ^{1}H NMR spectroscopy

entry	T	t_{HCl}	$t_{overall}$	yield (%)	product ratio **Z-7** : **1**
1	25 °C	2 h	74 h	74	100 : 0
2	50 °C	3 h	20 h	91	80 : 20
3	80 °C	3 h	3 h	89	73 : 27
4	100 °C	3 h	20 h	99	21 : 79
5	100 °C	5 h	125 h	91	5 : 95
6	110 °C	1 h	1 h	75	54 : 46



Z-7



Z-8

Tab. 2 Comparison of NMR spectroscopic data (ppm) of the aurons **Z-7** and **Z-8** (DMSO-d_6);

C/H	δ_C of **Z-7**	δ_C of **Z-8**	δ_H of **Z-7**	δ_H of **Z-8**
α	103.3	109.6	6.40	6.47
2	145.1	145.9		
3	179.2	179.1		
4	166.8	167.0		
5	97.6	97.7	6.05	6.09
6	167.4	167.5		
7	90.4	90.3	6.16	6.20
8	158.1	158.2		
9	95.7	102.9		
1'	109.8	123.7		
2'	138.7 [a]	123.9		7.18
3'	104.4	117.6	6.86	6.83
4'	149.2 [a]	147.4		
5'	151.8 [a]	145.5		
6'	116.5	115.9	7.48	7.41

[a]: assignment of the signals interchangeable

A prolonged reaction time at 50 °C led to an increase of the proportion of **1** (20% after 20 h, table 1, entry 2). Presumably, the *cis-trans* isomerization of **Z-7** to ***E*-7** initialized by protonation of the carbonyl group is the rate determining step: the hydroxyl groups at the benzofuranone nucleus interact with the carbonyl group *via* conjugation, ultimately increasing the isomerization barrier at the central olefinic bond, since the conjugation with the trihydroxyphenyl substituent becomes less important. Thus, higher temperatures as usual [7] are required for the *cis-trans*-isomerization: under optimized conditions (125 h at 100 °C, entry 5) an excellent yield of **1** is obtained. Obviously, ***E*-7** is rapidly transformed to *riccionidin A* (**1**) *via* intramolecular condensation and could not be detected in the reaction mixture.

The spectral data of synthetic *riccionidin A* (**1**) were compared with reported spectroscopic data (Table 3) [1a]. Some minor deviations (less than 0.3 ppm in the case of the ^{13}C NMR and less than 0.07 ppm in the case of the ^{1}H NMR spectrum) are explained by the different solvents used: the data for the natural sample was obtained in DMSO-d_6 with 0.5% DCl/D_2O (1:3), whereas we omitted DCl in order to avoid the H-D-exchange. However, a direct comparison of the IR-spectra and the UV-spectra confirms the identity of the natural and synthetic sample.

Tab. 3 Comparison of NMR spectroscopic data (ppm) of the natural sample of **1** (in 99.5% DMSO-d_6 + 0.5% DCl/D_2O in the ratio 1:3) with the synthetic sample (in DMSO-d_6); identification of the signals in analogy to lit. [1a];

C/H	δ_C of $\mathbf{1}_{nat}$	δ_C of $\mathbf{1}_{syn}$	δ_H of $\mathbf{1}_{nat}$	δ_H of $\mathbf{1}_{syn}$
1	*112.1*	*112.0*	*7.54*	*7.53*
2	147.9 [a]	147.9 [a]		10.83 (OH)
3	155.6 [a]	155.8 [a]		10.83 (OH)
4	103.1	103.3	7.64	7.58
4a	149.2	149.4		
5a	144.0 [a]	144.3 [a]		
5b	99.7	99.8		
6	157.9 [a]	157.9 [a]		12.51 (OH)
7	99.8 [b]	100.0 [b]	6.69 [c]	6.62 [c]
8	170.3 [a]	170.2 [a]		12.12 (OH)
9	91.4 [b]	91.6 [b]	6.74 [c]	6.73 [c]
9a	163.4 [a]	163.6 [a]		
10a	156.9 [a]	157.2 [a]		
11	127.1	127.0	9.06	9.07
11a	115.7		116.0	

[a]–[c]: assignments may be exchanged

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Experimental

All NMR spectra were measured in DMSO-d_6 as solvent (internal standard: ^{1}H NMR: δ/ppm(DMSO-d_5) = 2.50; ^{13}C NMR: δ/ppm DMSO-d_6) = 39.7): Bruker DRX 500. MS: MAT 311A. IR: Perkin Elmer 983. UV: Perkin Elmer 554.

4,6-Dihydroxy-2-[(2,4,5-trihydroxyphenyl)methyliden]-3(2H)-benzofuranone (**Z-7**)

Through a solution of 60.0 mg (0.39 mmol) of 2,4,5-trihydroxybenzaldehyde (**5**) [5] and 65.0 mg (0.39 mmol) of the benzofuranone **6** [6] in 4 ml acetic acid hydrogen chloride is bubbled during 2 h at room temperature. After 72 h additional stirring the precipitate is washed three times with 2 ml of water and dried for 5 h at 100 °C *in vacuo*: 87.0 mg (74%) of **Z-7** as a brownish red powder. – IR (KBr): ν/cm^{-1} = 3500–3020, 1653, 1619, 1568, 1456, 1381, 1304, 1212, 1187, 1163, 1071. – UV (ethanol): λ_{max} (lg ε)/nm= 210 (4.42), 250 (3.96, sh),

295 (3.87, sh), 330 (4.08), 429 (4.36). – ^{1}H NMR (500 MHz): δ/ppm = 6.05 (d, J = 1.7 Hz, lH, 5-H), 6.16 (d, J = 1.7 Hz, lH, 7-H), 6.40 (s, lH, α-H), 6.86 (s, lH, 3'-H), 7.48 (s, lH, 6'-H), 9.53, 10.75 (br, 5 H, 4-OH, 6-OH, 2'-OH, 4'-OH, 5'-OH). – ^{13}C NMR (125 MHz): δ/ppm = 90.35 (d, C-7), 95.73 (s, C-9), 97.64 (d, C-5), 103.33 (d, α-C), 104.43 (d, C-3'), 109.84 (s, C-l'), 116.49 (d, C-6'), 138.71 (s, C-2'), 145.12 (s, C-2), 149.22 (s, C-4'), 151.78 (s, C-5'), 158.12 (s, C-8), 166.76 (s, C-4), 167.40 (s, C-6), 179.18 (s, C-3). – MS (EI, 70 eV): m/z (%) = 302 (12) [M$^+$], 300 (5), 285 (6), 176 (37), 166 (21), 153 (21), 150 (39), 148 (16), 137 (12), 126 (100), 108 (14), 97 (9), 80 (28), 69 (30), 53 (27), 44 (72).

$C_{15}H_{10}O_7$ (302.24 g/mol) calcd.: C 59.61 H 3.33
$C_{15}H_{10}O_7$ + 1.5 H_2O: calcd.: C 54.72 H 3.98
found: C 54.80 H 3.60.

*2,3,6,8-Tetrahydroxybenzofuro[3,2-b][1]benzopyrylium chloride (riccionidin A, **1**)*

Through a solution of 1.0 g (6.5 mmol) of 2,4,5-trihydroxybenzaldehyde (**5**) [5] and 1.1 g (6.5 mmol) of the benzofuranone **6** [6] in 30 ml acetic acid hydrogen chloride is bubbled during 5 h at 100 °C. After 120 h additional stirring at 100 °C the reaction mixture is cooled to room temperature. The precipitate is washed with 5 ml of acetic acid and dried in vacuum: 1.89 g (91%) crude product consisting of 95% **1** and of 5% **Z-7** according to the ^{1}H NMR spectrum. A pure sample of **1** is obtained by recrystallization from ethanol containing 2% hydrochloric acid. **1** decomposes slowly at 150 °C. – IR (KBr): ν/cm^{-1} = 3500–3000, 2920, 2860, 1646, 1625, 1568, 1531, 1490, 1437, 1285, 1230, 1186, 1140, 1064. – UV (methanol/HCl [99.5:0.5]): λ_{max} (lg ε)/nm = 210 (4.38), 241 (4.43), 281 (4.00), 332 (3.60), 375 (3.61), 497 (4.46). – ^{1}H NMR (500 MHz): δ/ppm = 6.62 (d, J = 1.5 Hz, lH, 7-H), 6.73 (d, J = 1.5 Hz, lH, 9-H), 7.53 (s, 1H, 1-H), 7.58 (s, 1H, 4-H), 9.07 (s, 1H, 11-H), 10.83 (br, 2H), 12.12 (br, 1H), 12.51 (br, 1H). – ^{13}C NMR (125 MHz): δ/ppm = 91.63 (d, C-9), 99.84 (s, C-5b), 100.03 (d, C-7), 103.32 (d, C-4), 111.97 (d, C-1), 116.02 (s, C-11a), 126.96 (d, C-11), 144.26 (s, C-5a), 147.92 (s, C-2), 149.42 (s, C-4a), 155.78 (s, C-3), 157.17 (s, C-10a), 157.90 (s, C-6), 163.56 (s, C-9a), 170.17 (s, C-8); identification of the signals in analogy to the lit. [1a]. – MS (EI, 70 eV): m/z (%) = 285 (5), 164 (12), 163 (14), 150 (28), 126 (100), 108 (6), 97 (9), 80 (28), 69 (15), 52 (25), 51 (10), 48 (18), 44 (65).

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[9] For clarity the labels of the positions **Z-8** follow those of **Z-7**.

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